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L3: Entry 2 of 3

File: USPT

Aug 20, 2002

US-PAT-NO: 6436642DOCUMENT-IDENTIFIER: US 6436642 B1

TITLE: Method of classifying a thyroid carcinoma using differential gene expression

DATE-ISSUED: August 20, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gould-Rothberg; Bonnie E.	Guilford	CT		
Rastelli; Luca	Guilford	CT		

US-CL-CURRENT: 435/6; 435/320.1, 435/69.1

CLAIMS:

What is claimed is:

1. A method of categorizing a thyroid carcinoma in a subject, the method comprising: a) providing a test cell population from said subject, wherein at least one cell in said test cell population expresses the nucleic acid sequence MTC: 33; b) measuring the expression of MTC:33 in said test cell population; c) comparing the expression of MTC:33 to the expression of MTC:33 in a reference cell population comprising at least one cell whose thyroid carcinoma stage is known; and d) identifying a difference in expression levels of MTC33, if present, in the test cell population and reference cell population,

thereby categorizing said thyroid carcinoma in said subject.

2. The method of claim 1, wherein said carcinoma is a metastatic papillary thyroid carcinoma.

3. The method of claim 1, wherein an alteration of the expression of MTC:33 in said test cell population as compared to said reference cell population indicates that the test cell population has a different thyroid carcinoma stage than the cells in said reference cell population.

4. The method of claim 1, wherein a similar expression pattern of MTC:33 in said test cell population as compared to said reference cell population indicates that the test cell population has the same thyroid carcinoma stage as the cells in said reference cell population.

5. The method of claim 1, wherein said subject is a human.

6. The method of claim 1, wherein said reference cell population comprises a plurality of cells or a database.

7. The method of claim 1, wherein said thyroid carcinoma is a metastatic thyroid carcinoma.

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End of Result Set



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L2: Entry 4 of 4

File: USPT

Aug 20, 2002

DOCUMENT-IDENTIFIER: US 6436642 B1

TITLE: Method of classifying a thyroid carcinoma using differential gene expression

Detailed Description Text (73):

Also known as diamine acetyltransferase and putrescine acetyltransferase (genBank#m77693). It is a rate-limiting enzyme in the catabolic pathway of polyamine metabolism. It catalyzes the N (1)-acetylation of spermidine and spermine, and, by the successive activity of polyamine oxidase, spermine can be converted to spermidine and spermidine to putrescine. It is up-regulated in prostate cancer, and this up-regulation correlates with malignancy. (Saverio et al., Cancer Res 60(1):28-3400 (2000)). GENE CALLING.TM. analysis reveals that SSAT is up-regulated in metastatic vs. non-metastatic thyroid cancer.

Detailed Description Text (74):

Interestingly, for therapy considerations, increased transcription and ultimate superinduction of SSAT has been associated with the antineoplastic activity of several new antitumor polyamine analogues. (See Alhonen et al., Mol Pharmacol 55(4):693-8 (1999)). Potentially, polyamine analogues could have specific applications in the treatment of metastatic thyroid cancer.

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L8: Entry 1 of 1

File: PGPB

Nov 18, 2004

PGPUB-DOCUMENT-NUMBER: 20040229241

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040229241 A1

TITLE: Cloned mammalian polyamine oxidase

PUBLICATION-DATE: November 18, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Casero, Robert A.	Glenn Aron	MD	US
Wang, Yanlin	Baltimore	MD	US

APPL-NO: 10/733020 [PALM]

DATE FILED: December 12, 2003

RELATED-US-APPL-DATA:

Application 10/733020 is a continuation-in-part-of US application PCT/US02/18666, filed June 13, 2002, PENDING

Application is a non-provisional-of-provisional application 60/297815, filed June 13, 2001,

INT-CL-PUBLISHED: [07] C12Q 1/68, C07H 21/04, C12N 9/06

INT-CL-CURRENT:

TYPE	IPC	DATE
CIPP	<u>C12 N 9/06</u>	20060101

US-CL-PUBLISHED: 435/006; 435/069.1, 435/191, 435/320.1, 435/325, 536/023.2

US-CL-CURRENT: 435/6; 435/191, 435/320.1, 435/325, 435/69.1, 536/23.2

REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

Polynucleotides and the corresponding polypeptides of cloned mammalian polyamine oxidase (PAO) (including various isoforms and truncated forms) are provided. Also provided are antibodies to cloned mammalian PAO, and vectors and host cells containing cloned PAO, and methods for their use.

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<input type="checkbox"/>	L8	polyamine oxidase same lung cancer	1
<input type="checkbox"/>	L7	polyamine oxidase and lung cancer	16
<input type="checkbox"/>	L6	L4 and lung cancer	0
<input type="checkbox"/>	L5	L3 and l1	2
<input type="checkbox"/>	L4	L3 and l2	2
<input type="checkbox"/>	L3	6436642	3
<input type="checkbox"/>	L2	L1 and polyamine oxidase	4
<input type="checkbox"/>	L1	antitumor polyamine analog	4

END OF SEARCH HISTORY

=> file medline hcaplus biosis biotechds embase scisearch		
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=> s polyamine oxidase same lung cancer
 L1 0 POLYAMINE OXIDASE SAME LUNG CANCER

=> s PAOh1/SMO oxidase and lung cancer
 MISSING OPERATOR

=> s PAOh1SMO oxidase and lung cancer
 L2 0 PAOH1SMO OXIDASE AND LUNG CANCER

=> s PAOh1 oxidase and lung cancer
 L3 0 PAOH1 OXIDASE AND LUNG CANCER

=> s PAOh1 and lung cancer
 L4 13 PAOH1 AND LUNG CANCER

=> dup rem l4
 PROCESSING COMPLETED FOR L4
 L5 8 DUP REM L4 (5 DUPLICATES REMOVED)

=> d l5 1-8 ibib ab

L5 ANSWER 1 OF 8 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:1194616 SCISEARCH

THE GENUINE ARTICLE: 986PD

TITLE: Spermine oxidase SMO(PAOh1), not N-1-acetylpolyamine oxidase PAO, is the primary source of cytotoxic H2O2 in polyamine analogue-treated human breast cancer cell lines

AUTHOR: Pledgie A; Huang Y; Hacker A; Zhang Z; Woster P M; Davidson N E; Casero R A (Reprint)

CORPORATE SOURCE: Johns Hopkins Univ, Sidney Kimmel Comprehens Canc Ctr, 1650 Orleans St, CRB 409, Baltimore, MD 21231 USA (Reprint); Johns Hopkins Univ, Sidney Kimmel Comprehens Canc Ctr, Baltimore, MD 21231 USA; Wayne State Univ, Coll Pharm & Allied Hlth Profess, Dept Pharmaceut Sci, Detroit, MI 48202 USA
 davidna@jhmi.edu; rcasero@jhmi.edu

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2 DEC 2005) Vol. 280, No. 48, pp. 39843-39851.

ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650
ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 38
ENTRY DATE: Entered STN: 8 Dec 2005
Last Updated on STN: 8 Dec 2005

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The induction of polyamine catabolism and its production of H₂O₂ have been implicated in the response to specific antitumor polyamine analogues. The original hypothesis was that analogue induction of the rate-limiting spermidine/spermine N-1-acetyltransferase (SSAT) provided substrate for the peroxisomal acetylpolyamine oxidase (PAO), resulting in a decrease in polyamine pools through catabolism, oxidation, and excretion of acetylated polyamines and the production of toxic aldehydes and H₂O₂. However, the recent discovery of the inducible spermine oxidase SMO(PAOh1) suggested the possibility that the original hypothesis may be incomplete. To examine the role of the catabolic enzymes in the response of breast cancer cells to the polyamine analogue N-1, N(1-)bis(ethyl) norspermine (BENSpm), a stable knockdown small interfering RNA strategy was used. BENSpm differentially induced SSAT and SMO(PAOh1) mRNA and activity in several breast cancer cell lines, whereas no N-1-acetylpolyamine oxidase PAO mRNA or activity was detected. BENSpm treatment inhibited cell growth, decreased intracellular polyamine levels, and decreased ornithine decarboxylase activity in all cell lines examined. The stable knockdown of either SSAT or SMO(PAOh1) reduced the sensitivity of MDA-MB-231 cells to BENSpm, whereas double knockdown MDA-MB-231 cells were almost entirely resistant to the growth inhibitory effects of the analogue. Furthermore, the H₂O₂ produced through BENSpm-induced polyamine catabolism was found to be derived exclusively from SMO(PAOh1) activity and not through PAO activity on acetylated polyamines. These data suggested that SSAT and SMO(PAOh1) activities are the major mediators of the cellular response of breast tumor cells to BENSpm and that PAO plays little or no role in this response.

L5 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:203327 HCAPLUS

DOCUMENT NUMBER: 142:403615

TITLE: Induction of human spermine oxidase SMO(PAOh1)
) is regulated at the levels of new mRNA synthesis,
mRNA stabilization and newly synthesized protein
AUTHOR(S): Wang, Yanlin; Hacker, Amy; Murray-Stewart, Tracy;
Fleischer, Jennifer G.; Woster, Patrick M.; Casero,
Robert A., Jr.

CORPORATE SOURCE: The Sidney Kimmel Comprehensive Cancer Center, Johns
Hopkins University School of Medicine, Baltimore, MD,
21231, USA

SOURCE: Biochemical Journal (2005), 386(3), 543-547

CODEN: BIJOAK; ISSN: 0264-6021

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The oxidn. of polyamines induced by antitumor polyamine analogs has been assocd. with tumor response to specific agents. The human spermine oxidase, SMO(PAOh1), is one enzyme that may play a direct role in the cellular response to the antitumor polyamine analogs. In the present study, the induction of SMO(PAOh1) enzyme activity by CPENSpm [N1-ethyl-N11-(cyclopropyl)methyl-4,8,diazaundecane] is demonstrated to be a result of newly synthesized mRNA and protein. Inhibition of new RNA synthesis by actinomycin D inhibits both the appearance of SMO(PAOh1) mRNA and enzyme activity. Similarly, inhibition of newly synthesized protein with cycloheximide prevents analog-induced enzyme activity. Half-life detns. indicate that

stabilization of SMO(PAOh1) protein does not play a significant role in analog-induced activity. However, half-life expts. using actinomycin D indicate that CPENSpm treatment not only increases mRNA expression, but also leads to a significant increase in mRNA half-life (17.1 and 8.8 h for CPENSpm-treated cells and control resp.). Using reporter constructs encompassing the SMO(PAOh1) promoter region, a 30-90% increase in transcription is obsd. after exposure to CPENSpm. The present results are consistent with the hypothesis that analog-induced expression of SMO(PAOh1) is a result of increased transcription and stabilization of SMO(PAOh1) mRNA, leading to increased protein prodn. and enzyme activity. These data indicate that the major level of control of SMO(PAOh1) expression in response to polyamine analogs exposure is at the level of mRNA.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 1
 ACCESSION NUMBER: 2005237059 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15791459
 TITLE: Properties of recombinant human N1-acetylpolyamine oxidase (hPAO): potential role in determining drug sensitivity.
 AUTHOR: Wang Yanlin; Hacker Amy; Murray-Stewart Tracy; Frydman Benjamin; Valasinas Aldonia; Fraser Alison V; Woster Patrick M; Casero Robert A Jr
 CORPORATE SOURCE: The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA.
 CONTRACT NUMBER: CA51085 (NCI)
 CA85509 (NCI)
 CA88843 (NCI)
 CA98454 (NCI)
 SOURCE: Cancer chemotherapy and pharmacology, (2005 Jul) Vol. 56, No. 1, pp. 83-90. Electronic Publication: 2005-03-25. Journal code: 7806519. ISSN: 0344-5704.
 PUB. COUNTRY: Germany: Germany, Federal Republic of
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200507
 ENTRY DATE: Entered STN: 6 May 2005
 Last Updated on STN: 6 Jul 2005
 Entered Medline: 5 Jul 2005

AB The recent cloning of the mammalian gene coding for N(1)-acetylpolyamine oxidase (PAO) provides the opportunity to directly examine the role of human PAO (hPAO) in polyamine homeostasis as well as its potential role in determining cellular response to antitumor polyamine analogues. To facilitate the study of this enzyme, the production, purification, and characterization of the recombinant hPAO is reported. hPAO oxidizes N(1)-acetylspermidine ($K(m)=2.1 \text{ microM}$, $K(cat)=15.0 \text{ s}(-1)$) and has very high affinity for N(1)-acetylspermine ($K(m)=0.85 \text{ microM}$, $K(cat)=31.7 \text{ s}(-1)$). The recombinant hPAO does not efficiently oxidize spermine, thereby demonstrating a significant difference in substrate specificity from the previously described human spermine oxidase PAOh1/SMO. Importantly, hPAO demonstrates the ability to oxidize a subset of antitumor polyamine analogues; suggesting that this oxidase activity could have a significant effect on determining tumor sensitivity to these or similar agents. Transfection of A549 human lung cancer cells with an hPAO-expressing plasmid leads to a profound decrease in sensitivity to those analogues which act as substrates, confirming its potential to alter drug response. One similarity that hPAO shares with human PAOh1/SMO, is that certain oligoamine analogues are potent inhibitors of its oxidase activity. The results of these studies demonstrate how changes in polyamine catabolism may affect drug response.

L5 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:999597 HCAPLUS
 DOCUMENT NUMBER: 141:421055
 TITLE: Protein and cDNA sequences of human polyamine oxidase and their uses in tumor diagnosis and therapy
 INVENTOR(S): Casero, Robert A.; Wang, Yanlin
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 77 pp., Cont.-in-part of Appl. No. PCT/US02/18666.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004229241	A1	20041118	US 2003-733020	20031212
WO 2002100884	A2	20021219	WO 2002-US18666	20020613
WO 2002100884	A3	20030925		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-297815P P 20010613
 WO 2002-US18666 A2 20020613

AB The invention provides the protein and cDNA sequences of human polyamine oxidase (PAO) (including various isoforms and truncated forms). Also provided are antibodies to cloned mammalian PAO, and vectors and host cells contg. cloned PAO, and methods for their use. The invention also relates to a diagnostic or prognostic method for evaluating a response of a tumor to an antitumor polyamine analog by detecting expression of PAOh1/SMO oxidase or a splice variant. The invention further relates to a method for diagnosing a predisposition to cancer including prostate cancer, lung cancer, and breast cancer in a patient.

L5 ANSWER 5 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
 DUPLICATE 2

ACCESSION NUMBER: 2003:390455 BIOSIS
 DOCUMENT NUMBER: PREV200300390455
 TITLE: Microarray analysis uncovers retinoid targets in human bronchial epithelial cells.
 AUTHOR(S): Ma, Yan; Koza-Taylor, Petra H.; DiMattia, Debra A.; Hames, Lynn; Fu, Haoning; Dragnev, Konstantin H.; Turi, Tom; Beebe, Jean S.; Freemantle, Sarah J.; Dmitrovsky, Ethan [Reprint Author]
 CORPORATE SOURCE: Department of Pharmacology and Toxicology, Dartmouth Medical School, 7650 Remsen, Hanover, NH, 03755, USA
 ethan.dmitrovsky@dartmouth.edu
 SOURCE: Oncogene, (31 July 2003) Vol. 22, No. 31, pp. 4924-4932.
 print.
 ISSN: 0950-9232 (ISSN print).
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 27 Aug 2003
 Last Updated on STN: 27 Aug 2003
 AB Retinoids, the natural and synthetic derivatives of vitamin A, have a role in cancer treatment and prevention. There is a need to reveal mechanisms that account for retinoid response or resistance. This study identified

candidate all-trans-retinoic acid (RA) target genes linked to growth suppression in BEAS-2B human bronchial epithelial cells. Microarray analyses were performed using Affymetrix arrays. A total of 11 RA-induced species were validated by reverse transcription polymerase chain reaction (RT-PCR), Western or Northern analyses. Three of these species were novel candidate RA-target genes in human bronchial epithelial cells. These included: placental bone morphogenetic protein (PLAB), polyamine oxidase isoform 1 (PAOh1) and E74-like factor 3 (ELF3). Expression patterns were studied in RA-resistant BEAS-2B-R1 cells. In BEAS-2B-R1 cells, RA dysregulated the expression of the putative lymphocyte G0/G1 switch gene (GOS2), heme oxygenase 1 (HMOX1), tumor necrosis factor-alpha-induced protein 2 (TNFAIP2), inhibitor of DNA binding 1 (Id1), fos-like antigen 1 (FOSL1), transglutaminase 2 (TGM2), asparagine synthetase (ASNS), PLAB, PAOh1 and ELF3, while prominent induction of insulin-like growth-factor-binding protein 6 (IGFBP6) still occurred. In summary, this study identified 11 candidate RA-target genes in human bronchial epithelial cells including three novel species. Expression studies in BEAS-2B-R1 cells indicated that several were directly implicated in RA signaling, since their aberrant expression was linked to RA resistance of human bronchial epithelial cells.

L5 ANSWER 6 OF 8 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
 ACCESSION NUMBER: 2003:424605 SCISEARCH
 THE GENUINE ARTICLE: 679GH
 TITLE: Properties of purified recombinant human polyamine oxidase, PAOh1/SMO
 AUTHOR: Wang Y L; Murray-Stewart T; Devereux W; Hacker A; Frydman B; Woster P M; Casero R A (Reprint)
 CORPORATE SOURCE: Johns Hopkins Univ, Sch Med, Sidney Kimmel Comprehens Canc Ctr, Baltimore, MD 21231 USA (Reprint); SLIL Biomed Corp, Madison, WI 53711 USA; Wayne State Univ, Dept Pharmaceut Sci, Detroit, MI 48202 USA
 COUNTRY OF AUTHOR: USA
 SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (16 MAY 2003) Vol. 304, No. 4, pp. 605-611.
 ISSN: 0006-291X.
 PUBLISHER: ACADEMIC PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
 DOCUMENT TYPE: Article; Journal
 LANGUAGE: English
 REFERENCE COUNT: 42
 ENTRY DATE: Entered STN: 9 Jun 2003

Last Updated on STN: 9 Jun 2003

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The discovery of an inducible oxidase whose apparent substrate preference is spermine indicates that polyamine catabolism is more complex than that originally proposed. To facilitate the study of this enzyme, the purification and characterization of the recombinant human PAOh1/SMO polyamine oxidase are reported. Purified PAOh1/SMO oxidizes both spermine (K-m = 1.6 muM) and N-1-acetylspermine (K-m = 51 muM), but does not oxidize spermidine. The purified human enzyme also does not oxidize eight representative antitumor polyamine analogues; however, specific oligamine analogues were found to be potent inhibitors of the oxidation of spermine by PAOh1/SMO. The results of these studies are consistent with the hypothesis that PAOh1/SMO represents a new addition to the polyamine metabolic pathway that may represent a new target for antineoplastic drug development. (C) 2003 Elsevier Science (USA). All rights reserved.

L5 ANSWER 7 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
 ACCESSION NUMBER: 2004:28762 BIOSIS
 DOCUMENT NUMBER: PREV200400029514
 TITLE: Induction of the PAOh1/SMO polyamine oxidase by polyamine analogues in human lung carcinoma cells. ✓

AUTHOR(S): Devereux, Wendy; Wang, Yanlin; Stewart, Tracy Murray; Hacker, Amy; Smith, Renee; Frydman, Benjamin; Valasinas, Aldonia L.; Reddy, Venodhar K.; Marton, Laurence J.; Ward, Tracey D.; Woster, Patrick M.; Casero, Robert A. [Reprint Author]

CORPORATE SOURCE: Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA
rcasero@jhmi.edu

SOURCE: Cancer Chemotherapy and Pharmacology, (November 2003) Vol. 52, No. 5, pp. 383-390. print.
ISSN: 0344-5704 (ISSN print).

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 31 Dec 2003
Last Updated on STN: 31 Dec 2003

AB Purpose: The induction of polyamine catabolism has been directly associated with the cytotoxic response of various tumor types to the antitumor polyamine analogues. Initially, human polyamine catabolism was assumed to be under the control of a rate-limiting spermidine/spermine N1-acetyltransferase (SSAT) that provides substrate for an acetyl polyamine oxidase (PAO). We have recently cloned a new polyamine analogue-inducible human polyamine oxidase (PAO1/SMO) that efficiently uses spermine as a substrate. The induction of PAO1/SMO in response to multiple polyamine analogues was examined in representative lung tumor cell lines. Methods: Representatives of three different classes of antitumor polyamine analogues were examined for their ability to induce PAO1/SMO. Results: The human adenocarcinoma line, NCI A549 was found to be the most responsive line with respect to induction of PAO1/SMO in response to analogue exposure. Similar to previous observations with SSAT expression, PAO1/SMO induction was found to occur primarily in non-small-cell lung cancers cell lines. Using a series of polyamine analogues, it was found that the most potent inducers of PAO1/SMO possessed multiple three-carbon linkers between nitrogens, as typified by N1,N11-bis(ethyl)norspermine. Conclusions: Since PAO1/SMO is an analogue-inducible enzyme that produces H2O2 as a metabolic product, it may play a significant role in determining the sensitivity of various human tumors to specific polyamine analogues.

L5 ANSWER 8 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:285739 BIOSIS

DOCUMENT NUMBER: PREV200300285739

TITLE: The role of polyamine catabolism in anti-tumour drug response.

AUTHOR(S): Casero, R. A. Jr. [Reprint Author]; Stewart, T. M.; Devereux, W.; Hacker, A.; Wang, Y.; Smith, R.; Woster, P. M.

CORPORATE SOURCE: Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 1650 Orleans Street, Baltimore, MD, 21231, USA
rcasero@jhmi.edu

SOURCE: Biochemical Society Transactions, (April 2003) Vol. 31, No. 2, pp. 361-365. print.
CODEN: BCSTB5. ISSN: 0300-5127.

DOCUMENT TYPE: Article

LANGUAGE: English

OTHER SOURCE: DDBJ-AF226657; EMBL-AF226657; GenBank-AF226657;
DDBJ-NM153783; EMBL-NM153783; GenBank-NM153783

ENTRY DATE: Entered STN: 19 Jun 2003
Last Updated on STN: 1 Aug 2003

AB Interest in polyamine catabolism has increased since it has been directly associated with the cytotoxic response of multiple tumour types to exposure to specific anti-tumour polyamine analogues. Human polyamine catabolism was considered to be a two-step pathway regulated by the rate-limiting enzyme spermidine/spermine N1-acetyltransferase (SSAT) that provides substrate for an acetyl polyamine oxidase (APAO). Further, the super-induction of SSAT by several anti-tumour polyamine analogues has

been implicated in the cytotoxic response of specific solid-tumour phenotypes to these agents. This high induction of SSAT has been correlated with cellular response to the anti-tumour polyamine analogues in several systems and considerable progress has been made in understanding the molecular mechanisms that regulate the analogue-induced expression of SSAT. A polyamine response element has been identified and the transacting transcription factors that bind and stimulate transcription of SSAT have been cloned and characterized. The link between SSAT activity and cellular toxicity is thought to be based on the production of H₂O₂ by the activity of the constitutive APAO that uses the SSAT-produced acetylated polyamines. The high induction of SSAT and the subsequent activity of APAO are linked to the cytotoxic response of some tumour cell types to specific polyamine analogues. However, we have recently cloned a variably spliced human polyamine oxidase (PAO_{h1}) that is inducible by specific polyamine analogues, efficiently uses unacetylated spermine as a substrate, and also produces toxic H₂O₂ as a product. The results of studies with PAO_{h1} suggest that it is an additional enzyme in polyamine catabolism that has the potential to significantly contribute to polyamine homeostasis and drug response. Most importantly, PAO_{h1} is induced by specific polyamine analogues in a tumour-phenotype-specific manner in cell lines representative of the major forms of solid tumours, including lung, breast, colon and prostate. The sensitivity to these anti-tumour polyamine analogues can be significantly reduced if the tumour cells are co-treated with 250 µM of the polyamine oxidase inhibitor N1,N4-bis(2,3-butadienyl)-1,4-butanediamine (MDL 72,527), suggesting that the H₂O₂ produced by PAO_{h1} does in fact play a direct role in the observed cytotoxicity. These results strongly implicate PAO_{h1} as a new target that, in combination with SSAT, may be exploited for therapeutic advantage. The current understanding of the role and regulation of these two important polyamine catabolic enzymes are discussed.

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FILE 'MEDLINE, HCAPLUS, BIOSIS, BIOTECHDS, EMBASE, SCISEARCH' ENTERED AT 10:58:05 ON 27 OCT 2006

L1	0 S POLYAMINE OXIDASE SAME LUNG CANCER
L2	0 S PAOH1SMO OXIDASE AND LUNG CANCER
L3	0 S PAOH1 OXIDASE AND LUNG CANCER
L4	13 S PAOH1 AND LUNG CANCER
L5	8 DUP REM L4 (5 DUPLICATES REMOVED)

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	ENTRY	SESSION
FULL ESTIMATED COST	53.00	53.42
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-1.50	-1.50

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